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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MYRIAD GENETICS INC. LEGAL DEPARTMENT 320 WAKARA WAY SALT LAKE CITY, UT 84108				
EXAMINER LAMBERTSON, DAVID A				
ART UNIT		PAPER NUMBER		
1636		14		

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/040,964

Applicant(s)

MANFREDI ET AL.

Examiner

David A. Lambertson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 65-92 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 65-92 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4, 5. 6) ☐ Other: _____

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DETAILED ACTION

Election/Restrictions

In Paper No. 12, a previous examiner issued a restriction requirement for claims 65-92. Applicant's election with traverse of Group I (claims 65-76) in Paper No. 13 is acknowledged. The traversal is on the ground(s) that a search of all the claims would not be burdensome to the examiner. Applicant's arguments are convincing, thus the previous Restriction requirement is vacated.

Claims 65-92 are ready for examination in the instant application.

Priority

Applicant's claim for domestic priority to US Application No. 60/259,759 under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

The information disclosure statements filed July 1, 2002 and September 13, 2002 have been considered, and a signed and initialed copy of the form PTO-1449s are attached to this Office Action. It is noted that the IDS filed July 1, 2002 indicates US Patent Applications. These references have been considered by the Examiner (as evidenced by the double-patenting rejection), but have been crossed through on the form PTO-1449. This is because it is improper to print US Application numbers on an issued patent.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 65-89 and 92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 65, 66, 79, 80 and 85 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to recite a positive process step that refers back to the preamble of the claim. In order for the claimed method to be definite in terms of the metes and bounds of the invention, the claim must recite a method step that provides for the result of the methods as claimed. Amending the claims to contain the statement “thereby detecting a protein-protein interaction” at the end of the claim would be remedial.

Claims 67, 72-75 and 92 contain the limitation “to at least partially anchor to the cell membrane.” This limitation is indefinite because it is unclear what constitutes partially anchored to the cell membrane. It would seem that the protein is either anchored to the cell membrane, or is not anchored to the cell membrane; there does not seem to be a situation where the protein is sometimes anchored, but sometimes not anchored. It would be remedial to indicate that the protein anchors to the cell membrane by removing the limitation “partially.”

Claim 89 is inconsistent with the claim from which it depends (i.e., claim 85). In claim 85, the limitations indicate that the prey fusion protein comprises the C-intein, and the bait fusion protein comprises the N-intein. However, in claim 89, the fusion proteins are inverted, indicating that the prey fusion protein comprises an N-intein while the bait fusion protein

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comprises the C-intein. It would be remedial to properly indicate that the prey fusion protein comprises a C-intein while the bait fusion protein comprises the N-intein, consistent with the limitations of claim 85.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 65-70, 72 and 90-92 are rejected under 35 U.S.C. 102(a) as being anticipated by Ozawa *et al.* (IDS reference B11; see entire document; henceforth Ozawa).

Ozawa teaches a method of detecting protein-protein interactions in bacterial (*E. coli*) host cells using two fusion/chimeric proteins. The first fusion protein (which can be either a bait protein or a prey protein, interchangeably) comprises an inactive N-terminal portion of the fluorescent protein EGFP (which is not an endogenous gene in *E. coli*), fused to the N-terminus of an N-intein fragment (the *S. cerevisiae VDE* gene), which is then fused to the N-terminus of the bait/prey protein, specifically the membrane bound receptor protein CaM/calmodulin (see for example the Abstract and page 5153, Figure 2). The second fusion protein (which can also be either a bait protein or a prey protein, interchangeably) comprises the remaining inactive C-terminal portion of the fluorescent protein EGFP, fused to the C-terminus of a C-intein fragment (the *S. cerevisiae VDE* gene), which is then fused to the C-terminus of the bait/prey protein, specifically the CaM/calmodulin binding protein M13 (see for example the Abstract and page

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5153, Figure 2). Because the bait and prey proteins are interchangeable (the characterization of a protein as a bait or prey is determined semantically), either protein can be fused to the N-intein or C-intein and *vice versa*. These fusion proteins are cloned into the pET vectors which have known multi-cloning sites (MCS), therefore Ozawa also anticipates kits comprising the vectors encoding the aforementioned fusion proteins. Upon the interaction of the bait and prey proteins, the intein fragments properly fold, resulting in the protein splicing event and resulting in the production of a functional EGFP protein which can be detected, thereby indicating a protein-protein interaction (see for example the Abstract and page 5132, Figure 1). Ozawa further teaches that this technique can be used to screen expression libraries for unknown protein interactions similar to the way a yeast two-hybrid system is used (see for example the Abstract and page 5151, first paragraph). This technique gives the strong advantage of a highly sensitive detection assay (see for example page 5156, right column, last paragraph) as well as a way to visualize any protein-protein interaction in living animals (see for example page 5157, last paragraph).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 71, 80, 81, 85 and 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ozawa as indicated in the rejection of claims 65-70 and 72, in view of Michnick *et al.* (US

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Patent No. 6,294,330; see entire document; henceforth Michnick), in further view of Brent *et al.* (IDS reference A8; see entire document; henceforth Brent).

Ozawa teaches all of the elements set forth above in the rejection of claims 65-70 and 72. However, although Ozawa indicates that their technique can be used to detect protein-protein interactions in a manner similar to that of a yeast two-hybrid system (i.e., using the technique to test the interaction of members of expression libraries), Ozawa does not specifically teach the use of yeast as a host cell. Similarly, Ozawa does not teach mating two yeast cells so as to introduce the two fusion proteins into the same cellular environment to promote their interaction.

Michnick teaches a method where a reporter protein (e.g., a fluorescent protein) is physically separated into two inactive fragments, but can be reconstituted when the inactive portions are fused to heterologous proteins that interact (see for example Column 5, line 66 to column 6, line 33). The purpose of this method is to detect protein-protein interactions by virtue detecting the reconstituted reporter molecule, for example between members of an expression/cDNA library (see for example the Abstract,). Michnick further teaches that this method can be practiced in a wide range of host cells, including bacteria and yeast (see for example column 20, line 64 to column 21, line 12). Although Michnick provides the general teaching that an inactivated protein can be re-activated by fusing the inactive fragments to proteins that are known to interact, and that this technique can be used from bacteria to yeast, Michnick does not provide teachings regarding the mating of yeast to bring the fusion proteins into an interacting environment.

Brent teaches a general method of detecting protein-protein interactions by using fusion proteins, utilizing the mating of yeast to introduce the fusion proteins into the same environment

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(see for example the Abstract and column 2, lines 3-19). This method allows large number of individual protein-protein interactions to be measured (see for example column 7, lines 56-65).

It would have been obvious to combine the teachings of Ozawa and Michnick because both methods involve the detection of protein-protein interactions by reconstituting inactivated fragments of a reporter gene; therefore the teachings are inextricably related by purpose and method. The ordinary skilled artisan would have been motivated to combine these teachings in order to increase the range of host cells that could be used in practicing the invention, as taught by Michnick through the use of host cells besides the bacterial host cells described by Ozawa. Absent evidence to the contrary, the skilled artisan would have had a reasonable expectation of success when practicing the claimed invention.

It would have been obvious to combine the teachings of Ozawa in view of Michnick with those of Brent because each of the teachings involves the detection of protein-protein interactions using yeast host cells. The ordinary skilled artisan would have been motivated to combine the teachings of Ozawa in view of Michnick with those of Brent in order to measure the interactions between a large number of individual proteins, as taught by Brent. Absent evidence to the contrary, the skilled artisan would have had a reasonable expectation of success when practicing the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686

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F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 65, 66, 90 and 91 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 23 of U.S. Patent No. 6,562,576 (henceforth the '576 patent). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are generic claims that are anticipated by the specific claims set forth in the '576 patent. Specifically, the instant claims are directed to a kit and a method of detecting a protein-protein interaction in a host cell, which comprises the detection of protein-protein interactions in yeast cells. The '576 patent claims an identical kit and method of detecting a protein-protein interaction, with the exception that the host cell that is used is more narrowly claimed as "yeast cells" and the kit contains instructions. However, as indicated above, "yeast cells" are a species of a host cell, and thus anticipate the instantly claimed invention. Furthermore, the "instructions for use" are an intended use limitation, and do not convey any patentable utility on the claimed invention. Because the claims of the '576 patent anticipate the instant claims 65, 66, 90 and 91, the instant claims constitute an obviousness-type double patenting.

Allowable Subject Matter

No claims are allowable.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
AU 1636



**JAMES KETTER
PRIMARY EXAMINER**